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10/521,691	08/31/2005	Masayasu Okochi	10873.1604USWO	4565

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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,691	OKOCHI ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *6-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-10* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/23/05;3/13/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Revised Notice; PTO-90C*.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-5, drawn to a novel polypeptide derived from a Notch polypeptide in the reply filed on 26 March 2008 is acknowledged. The traversal is on the ground(s) that the Okochi reference cited to support the restriction was published less than one year prior to the international filing date and subsequent to the Japanese priority date claimed by the present application. This is not found persuasive because Okochi et al. (EMBO J. 271(20): 5408-5416, October 2002) is considered prior art (categorized as an "X, P" reference in an international search report). Additionally, claim 1 is anticipated by Mumm et al. (Mol Cell 5: 197-206, 2000) (see 102 rejections below). Thus, claim 1 lacks a special technical feature and cannot share one with the other claims.

The requirement is still deemed proper and is therefore made FINAL.

Claims 6-10 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 26 March 2008.

Claims 1-5 are under consideration in the instant application.

Sequence Compliance

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). **Specifically, the sequences disclosed in Figures 4A-4B and 6B are not accompanied by the required reference to the relevant sequence identifiers. Additionally, the specification**

discloses primer sequences at page 7 that are not accompanied by the required reference to the relevant sequence identifiers. This application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825).

Information Disclosure Statement

2. The information disclosure statement filed 23 May 2005 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered (Okocki et al. 2001 and Kageyama et al. 2000).

Claim Objections

3. Claims 1, 4, and 5 are objected to because of the following informalities:

3a. In claim 4, line 5, a period is missing at the end of the claim.

3b. In claim 1, line 3, amend "a nucleus" to recite "the nucleus of a cell".

3c. Claims 4 and 5 use the acronyms "S3" and "S4" without first defining what they represent in the independent claims. While the claims can reference acronyms, the material presented by the acronym must be clearly set forth at the first use of the acronym.

3d. In claim 1, line 1, the term "novel" should be deleted.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 1-5 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. Claims read on a product of nature in that the claimed polynucleotide is not "isolated". In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty,* 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" or "purified" as taught by pages 11-12 of the specification. See MPEP 2105.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. The term "series of proteolytic events" in claims 1-5 is a relative term which renders the claims indefinite. The term "series of proteolytic events" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what processes or steps are encompassed by this phrase.

7. Claims 1-5 are indefinite because claim 1 recites the limitation "extracellular proteolysis" in line 4. There is insufficient antecedent basis for this limitation in the claim.

8. The term "derived" in claim 1, line 1 is a relative term which renders claims 1-5 indefinite. The term "derived" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear if the term "derived" means that the polypeptide is a fragment, mutant, homolog, etc.

9. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). Regarding claims 4 and 5, in the present instance, claim 4 recites the broad recitation "proteolysis", and the claim also recites "S4 cleavage" which is the narrower statement of the range/limitation. Claim 5 recites the broad recitation "cleavage site" and the claim also recites "S4" which is the narrower statement of the range/limitation.

10. Claims 4 and 5 are indefinite because it is not clear what the term "S3" is referring to in the claims. The specification discloses a "S3 cleavage site" (for example, page 5, lines 1-6).

However, it is not clear if the claims are referring to the "S3 cleavage site" or an amino acid at a particular position.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is directed to a polypeptide derived from a Notch protein, wherein in a series of proteolytic events of the Notch protein, the polypeptide is released to an extracellular space when NICD translocates to a nucleus as a result of intramembranous endoproteolysis that occurs subsequent to extracellular proteolysis. Claim 2 recites that the polypeptide is released to the extracellular space in proportion to Notch signal transduction. Claim 3 recites that the release of the polypeptide to the extracellular space results from presenilin-dependent proteolysis. Claim 4 recites that proteolysis of the Notch protein occurs silmultaneously with or either before or after proteolysis at S3, the proteolysis (S4 cleavage) occurring on a N-terminal side with respect to the S3 in a transmembrane domain of the Notch protein. Claim 5 recites that the S4 cleavage site on the N-terminal side with respect to the S3 is an amino acid residue in the transmembrane doman.

The specification of the instant application teaches in a series of proteolytic events of the Notch protein, the polypeptide is released to an extracellular space when NCID translocates to a nucleus as a result of the intramembranous endoproteolysis that occurs subsequent to the extracellular proteolysis (page 3, lines 1-5). The specification discloses that there are several types of novel polypeptide with their C-termini being different from each other and is hereinafter referred to as Notch-β (Nβ) (page 3, lines 9-14). The specification teaches that the Nβ polypeptide includes an amino acid sequence selected from SEQ ID NOs: 1-18 (page 5, lines 7-9).

However, the claims of the instant application do not require that the polypeptide possesses any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include actual reduction to practice, disclosure of drawings or structure chemical formulas, sufficient relevant identifying characteristics (such as, compete or partial structure, physical and/or chemical properties, and functional characteristics when coupled with a known or disclosed structure/function correlation), methods of making the claimed product, level of skill and knowledge in the art, predictability in the art, or any combination thereof. In this case, the specification has not shown a relationship between the structure and function of the genus of polypeptides recited in the claims. Therefore, since there are no sufficient identifying characteristics of the polypeptide recited in the claims, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

Thus, the skilled artisan cannot envision the detailed chemical structure of the polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. **Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The polypeptide itself is required**. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Additionally, a biomolecule sequence described only by a functional characteristic (i.e. more highly expressed), without any known or disclosed correlation between the biological function and the structure of the sequence is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. *In re Bell* F.2d 781, 26 USPQ2d (Fed. Cir. 1993).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a specific Notch-β polypeptide, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

12. Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Mumm et al. (Mol Cell 5: 197-206, 2000). It is noted that claim 1 has been broadly interpreted by the Examiner as reading upon any isolated extracellular domain of Notch made by any means.

Mumm et al. teach that activated Notch proteins and the full-length receptor responding to ligand binding are cleaved at a novel proteolytic site, termed S2, within the extracellular juxtamembrane region of Notch (abstract; page 202, column 2, first full paragraph; Figures 1, 2 and 6). The resultant carboxyl product is termed, NEXT (Notch extracellular truncation) (page 197, column 2, 2nd full paragraph). Mumm et al. disclose that NEXT is isolated for N-terminal sequencing (page 205, column 2, first full paragraph).

13. Claims 1-5 are rejected under 35 U.S.C. 102(a) as being anticipated by Okochi et al. EMBO J. 271(20): 5408-5416, October 2002.

Okochi et al. teach polypeptides, termed N-terminal Notch-1 Aβ-like fragments (Nβ), that are derived from a Notch protein (abstract; page 5409, bottom of column 1 through the top of column 2; page 5411, Table I). Okochi et al. disclose that the release of the fragments into the extracellular space is presenilin (PS)/gamma-secretase dependent (abstract; page 5409, column 2, first full paragraph). Okochi et al. teach that the Nβ fragment is cleaved at a novel site (site-4, S4), near the middle of the transmembrane domain of Notch-1 (abstract; page 5409, bottom of column 1 through the top of column 2; Figure 2B). Okochi et al. disclose that the order of the cleavages (S3 and S4) are not known (page 5412, column 1, 2nd full paragraph).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Lammich et al. J Biol Chem 277 (47): 44754-44759, 2002.

Zhang et al. J Biol Chem 277(17): 15069-15075, 2002.

Okochi et al. J Biol Chem 281(12): 7890-7898, 2006.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
10 June 2008

/Bridget E Bunner/
Primary Examiner, Art Unit 1647